ANKYLOSING SPONDYLITIS TREATED WITH CORTISONE AND ALLIED SUBSTANCES

BY

C. R. CROFT, T.D., D.M., M.R.C.P.*Physician, South Devon and East Cornwall Hospital, Plymouth*

The use of cortisone and allied substances in the treatment of ankylosing spondylitis has received little attention. A recent leading article on prednisone and prednisolone (*British Medical Journal*, 1957) makes no reference to it. In this country, West and Newns (1954) report symptomatic benefit in six cases treated with corticotrophin for 18 to 30 months, but regard it as justified only in the most severe cases. Hart (1952, 1955) showed rapid symptomatic improvement in three out of six cases, but regarded it as suitable only for acute painful episodes. In America, ankylosing spondylitis is regarded as part and parcel of rheumatoid arthritis, and very little specific information on spondylitis is available. Copeman (1953) records Boland as writing that cortisone is highly effective in suppressing rheumatoid spondylitis and that most cases can be kept under control with cortisone maintenance dosage, although he regards it as second choice to x-ray therapy. Forestier *et al.* (1956) record the use of cortisone in doses of 100–150 mg. for periods of 20 to 40 days over six to eight months. They suggest that its use should be reserved for very severe cases and for patients with persistent peripheral involvement.

The general argument for and against long-term treatment with cortisone and its allies in rheumatic diseases is still inconclusive. Whatever may be one's opinion of their therapeutic value, it seems that, on grounds of safety, their use for relief of persistent pain is justified, provided certain types of patient are excluded, simple precautions are taken, and the patients are kept under occasional observation.

A long period usually elapses between the onset of symptoms and firm diagnosis and treatment. The most satisfactory figures are secured in the Services, where Baird (1955) and Morrison (1955) record that half their cases were diagnosed within two years. In the present series of 14 cases only five were diagnosed in four years or less. The patient has had little to lose from this in the past, but earlier diagnosis will be desirable if rapid and sustained relief can be provided.

I am therefore encouraged to record the symptomatic effect of treating with these substances 14 consecutive cases of ankylosing spondylitis in which the diagnosis had long been established and in which orthodox treatment, including radiotherapy, sometimes given to the limit of safety, had been abandoned. A few patients were in hospital in the early stages of treatment, but most were dealt with as out-patients and were seen first at intervals of two to four weeks, and later of three months.

Corticotrophin (long-acting, when available) was employed in earlier cases in doses of 10–25 units, once or twice daily according to supply and symptomatic response. Later, cortisone was used in doses of 50–100 mg. daily, but recently this has been replaced by prednisolone up to 15 mg. daily. The last appears to be the most effective and least liable to cause moon-face.

Estimation of the response rests almost entirely on the patient's observations.

The least that can be said is that some relief has been given when other forms of treatment have been abandoned. In the early stages the disease may show long periods of spontaneous remission, and further experience is needed to decide whether corticotrophin or cortisone compounds should be employed to tide patients over the acute phases, without resort to other treatment.

Case Reports

Case 1.—An accountant aged 47 had had symptoms for 12 years. In October, 1953, gross kyphosis was present with fusion of the whole spine and both hip-joints and very limited shoulder movement. He was no longer able to see a client sitting in front of him. He was in great pain, very thin, and had been unable to work for some months. His E.S.R. was 54 mm. in 1 hour. Previous treatment had consisted of a spinal jacket in the early years and occasional physiotherapy later. Corticotrophin was given continuously from November, 1953, until his death from cor pulmonale in December, 1955. Within a week of starting treatment he experienced almost complete relief of pain and substantial improvement in shoulder movement, which enabled him to brush his hair once more. His sleep and appetite improved and his weight increased. He resumed work, and in February, 1954, felt well enough to wish to join a sailing club, and indeed this was arranged. He remained reasonably free of pain and worked at home almost continuously until his death. All concerned—the patient, his wife, and his doctor—considered the treatment was well worth while despite the difficulties associated with it.

Case 2.—A man aged 34 had had symptoms for 11 years. In May, 1955, he was admitted to hospital and lay flat in bed with severe pains in the back, the sacro-iliac joints being mainly affected. His E.S.R. was 30 mm. in 1 hour. Previous treatment included four courses of x-ray therapy between 1949 and 1954, without much benefit. Within four days of starting corticotrophin gel he was up and about the ward and was discharged after one week, having been taught to give his own injections. He varied the dosage, between 15 and 25 units twice daily, to secure adequate relief of symptoms. Corticotrophin was continued until October, 1956, and since then he has taken prednisolone, 10–15 mg. daily. Since August, 1955, he has worked continuously as a maintenance engineer. He gets some pain when digging in his garden. With an effort he can touch his toes without discomfort. In February, 1957, his E.S.R. was 15 mm. in 1 hour.

Case 3.—A man aged 29, who had had symptoms for one year, was seen in July, 1955, with fusion of sacro-iliac joints, some kyphosis, painful dorsal spine, general weakness, and inability to work for the previous month. His E.S.R. was 43 mm. in 1 hour. No previous treatment had been given. Corticotrophin was started in July, with relief of pain and some increased mobility within one week. He returned home after two weeks, having been taught to give his own injections, and he resumed light work. He was readmitted in December with melaena from duodenal ulcer. Corticotrophin was stopped, with some recurrence of pain. He resumed work in February, 1956, with slight pain, which gradually abated, and until December he worked 10 hours a day as a market gardener. He could touch his toes, but extension of the lumbar spine was defective. In September, 1956, his E.S.R. was 17 mm. in 1 hour. Since January, 1957, pain has recurred, and further treatment with cortisone is at present precluded by the peptic ulcer, which is causing symptoms.

Case 4.—A woman aged 59, who had had symptoms for 11 years, was seen in 1955 with a straight rigid back and fixed hips, slight shoulder movement, poor general condition, mental depression, much pain, especially at night, and serious disturbance of sleep; also a large leg ulcer and oedema of legs. Corticotrophin gel, 20 units daily, was given from

July, 1955, to September, 1956; cortisone, 25 mg. twice daily, from then onwards. She reported that as soon as treatment began her pain was relieved and she slept well, her appetite and general health improved, and movement in the neck and shoulders increased. She is now a contented person, free of pain and able to take a lively interest in her household, and in recent months treatment of her leg ulcer has resulted in healing. She is very satisfied. She has been treated entirely at home.

Case 5.—A man aged 35, who had had symptoms for six years, was seen in 1955 with a rigid lumbar and dorsal spine, complaining of considerable pain in his back and buttocks, particularly for the previous seven months. He was also suffering from chronic non-specific colitis. His E.S.R. was 58 mm. in 1 hour. Previous treatment had consisted of physiotherapy. Corticotrophin gel, 10 units twice daily, was started on August 4, with immediate relief of all pain attributable to spondylitis and considerable improvement in the colitis and in general nutrition. After instruction in giving his own injections he was discharged from hospital on August 10 and resumed work shortly afterwards. Corticotrophin was maintained until September, 1956, with freedom from pain except when he ran short of the drug. It was replaced by prednisolone in September, 1956, and he was free of pain and at work when last seen in October, 1956, shortly before leaving the district, although colitis continued to cause disability. He developed some degree of moon-face, but preferred this to the pain.

Case 6.—A man aged 54, who had had symptoms for 10 years, was seen in November, 1955, with a rigid spine, slight deformity, chest expansion of 1 in. (2.5 cm.), and considerable pain in the back and chest, especially at night. In March, 1955, the E.S.R. was 9 mm. in 1 hour. He was receiving 100% disability pension. X-ray therapy had been given in 1951, and supplementary treatment in 1952, with improvement. In 1953 further x-ray therapy was considered inadvisable. Cortisone was started in November, 1955, and one month later he reported that pain was less and mobility had increased. He has continued under the care of his doctor, who tells me that he applies regularly for further supplies of cortisone, which he finds very effective in relieving his pain.

Case 7.—A man aged 65 had had symptoms for 40 years, but had received no previous treatment. His spine was kyphotic and rigid from sacrum to occiput, and he complained of pain in his shoulders and down his back. His E.S.R. was 64 mm. in 1 hour. Cortisone was started on December 1, 1955. Three weeks later he reported that the feeling of stiffness was much reduced and that he had more freedom of movement. In May, 1956, the pain was slight and activity was greatly improved; this was confirmed by his wife. In October, he reported no pain. His E.S.R. was then 60 mm. in 1 hour. In February, 1957, freedom from pain and increased activity were maintained.

Case 8.—A woman aged 45 had had symptoms for 15 years. The whole spine below the neck was completely rigid with long thoracic kyphosis. Severe pain was present in shoulders and neck, and she wore a brace. Her E.S.R. in October, 1955, was 23 mm. in 1 hour. Cortisone was given from December, 1955, to March, 1956. She said she was free of pain within 10 days of starting this and that her neck moved more freely. Improvement was maintained after stopping cortisone. In January, 1956, she said, "I feel better than I have done for years." Her E.S.R. was 12 mm. in 1 hour. In October she reported that she felt well and had no pain, and she considered that her neck movement had greatly improved. In February, 1957, improvement was maintained. Her E.S.R. was then 26 mm. in 1 hour.

Case 9.—A man aged 25, who had had symptoms for four years, was seen in April, 1956, complaining of pain, mainly in the buttocks and down the backs of both legs. There was limited movement of the lumbar and thoracic spine, with x-ray changes of ankylosing spondylitis in the sacro-iliac joints. His E.S.R. was 20 mm. in 1 hour. X-ray

therapy from October, 1955, to January, 1956, had provided some relief. Cortisone was started in April, 1956, and in May he said that the pain was less and in June that it was negligible. The dose of cortisone was reduced and the drug was stopped in September. In November he said, "I am one hundred per cent.," and examination showed a good range of painless flexion and extension of his spine. In February, 1957, the improvement was maintained. His E.S.R. was then 16 mm. in 1 hour.

Case 10.—A man aged 28, who had had symptoms for 14 years, was seen in June, 1956, with dorsal kyphosis and very restricted spinal movements, including the neck, which was very painful. Fair shoulder movement was present, but with much pain; elbows were painful and stiff; hips showed a fair range of painful movement; chest expansion was 1½ in. (3.8 cm.); E.S.R. was 36 mm. in 1 hour. X-ray therapy had been given in 1949 and 1952, on both occasions with considerable benefit; also in 1954 and 1956, after which further exposure was thought to be inadvisable. Prednisolone, 5 mg. three times a day, was started on June 30, 1956. On July 4 he reported freedom from pain and improved neck movement, and his chest expansion was 2½ in. (5.7 cm.). He was discharged from hospital. On July 10 he was fit to resume work and the dose of prednisolone was reduced to 5 mg. daily. In November he reported that the improved mobility was maintained but that he had slight pain, and the dose of prednisolone was restored to 5 mg. three times a day. In February, 1957, he reported that "by and large, the tablets keep me free of pain." His E.S.R. was then 5 mm. in 1 hour.

Case 11.—A woman aged 43, who had had symptoms for nine years, was seen in June, 1956, complaining of pain and stiffness in the lumbar region and in the neck and shoulders. She was kyphotic, with rigid lumbar and dorsal spine but with some cervical movement. Chest expansion was greatly restricted. Her hips showed a full range of painless movement. Her general nutrition was poor. Her E.S.R. was 25 mm. in 1 hour. She had received x-ray therapy for her sacro-iliac joints in 1950 and for her cervical spine in 1954, with improvement, and again in January and February, 1956. Cortisone was given in June for one month, during which she said she "felt really well" and that her pain was greatly eased; she thought her mobility had increased. She relapsed after ceasing cortisone, but improvement again occurred when prednisolone was started in September. In February, 1957, she said she felt well, had been almost entirely free of pain, and her neck was more freely movable. She was going out to work as well as looking after her own household. Her E.S.R. was 12 mm. in 1 hour.

Case 12.—A man aged 35, who had had symptoms for 14 years, was seen in July, 1956, with a rigid spine and upper dorsal kyphosis. His shoulders allowed his arms to be raised to the horizontal line and were painless; his hips showed a good range of movement but with much stiffness and pain, especially in the morning. His E.S.R. was 30 mm. in 1 hour. Previous treatment consisted of x-ray therapy in 1946 and in 1950-1, with supplementary treatment 1954 and 1955. Prednisolone was started in July, 1956. In August he reported almost complete freedom from pain, no stiffness on waking, and good hip movement. In October he was free of pain, and reported greatly improved general capacity for movement. In February, 1957, he reported continued freedom from pain and from the feeling of stiffness. His E.S.R. was 7 mm. in 1 hour. He had worked continuously as a clerk.

Case 13.—A man aged 27 had had symptoms for five years. In June, 1956, he had a well-developed dorsal kyphosis and wore a brace; he complained of considerable pain in the back, buttocks, and neck. His E.S.R. was 15 mm. in 1 hour. X-ray therapy (900 r) had been given in 1953 without effect on his pain. Prednisolone was started in July, 1956. One month later he reported that he was "much better but has slight neck pain." It was then possible to tighten his brace. In October his chest expansion was 2 in. (5 cm.) against 1 in. (2.5 cm.) in June. In February,

1957, he said he was much better since taking the tablets, and that he was reminded by discomfort if he did not take them. He has worked regularly during treatment.

Case 14.—A man aged 53 had had symptoms for 30 years. In October, 1956, he had a straight rigid dorsal and lumbar spine and slight movement of his neck, which was projected forward. His ribs showed no appreciable movement during respiration. Lumbar spine and sacro-iliac joints were completely ankylosed. His E.S.R. was 25 mm. in 1 hour. He complained of considerable pain in his shoulders and neck. Prednisolone was started in October, and one month later he reported that he was "practically free of pain—more so than for six or seven years"; also that movement of his neck had improved and he felt fully active. His chest expansion was then 1 in. (2.5 cm.). In February, 1957, he reported that pain was negligible, and he thought that movement of his neck had further improved. His chest expansion was 1½ in. (3.8 cm.). He had worked continuously as a schoolmaster. His E.S.R. was 5 mm. in 1 hour.

Summary

The response of 14 consecutive patients with advanced and painful ankylosing spondylitis to treatment with corticotrophin, cortisone, and prednisolone is recorded. There has been an appreciable degree of relief of symptoms, which had not been obtained by other means. The relief of pain was rapid, and was accompanied by some increased freedom of movement. In some cases treatment was stopped, with continuing relief.

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ADRENOCORTICAL HYPERACTIVITY IN A PATIENT WITH BRONCHIAL CARCINOMA AND DIABETES MELLITUS

BY

F. D. ROSENTHAL, M.D., M.R.C.P.

Senior Medical Registrar, Royal Infirmary, Sheffield

Adrenal hyperplasia has been reported to be present at necropsy in about 6% of all patients dying with malignant disease, and appears to be associated most commonly with carcinoma of the bladder, endometrium, kidney, and respiratory tract (Parker and Sommers, 1956). Dobriner (1952) showed that in cases of cancer the mean urinary corticosteroid excretion was higher than normal, and Voigt and Kny (1954) recorded a case of bronchial carcinoma with increased insulin tolerance. The interest in the present case lies in the occurrence of marked adrenocortical hyperactivity in association with bronchial carcinoma.

Case Report

A 48-year-old furnaceman was admitted to hospital on May 17, 1955. For many years he had suffered from a cough with some mucoid sputum which he attributed to smoking about 15 cigarettes a day. In March, 1955, he had a short

febrile illness, following which he failed to regain his strength. His mouth and tongue felt dry; he drank a great deal of fluid and passed large quantities of urine at frequent intervals. His appetite decreased, he lost weight, and for one week prior to admission took no solid food. Progressive pigmentation appeared on the face and arms. For two weeks his ankles had been swollen, and he noticed tingling in his fingers and toes. Throughout this period he was troubled by an unproductive cough.

Examination showed him to be a well-built muscular individual with evidence of recent weight loss. A bluish-brown pigmentation affecting the skin and buccal mucous membranes was most pronounced on the face and extensor surfaces of the arms. The skin and tongue were dry; the sputum was mucoid. At the right lung base the percussion note was decreased and air entry diminished. The liver was enlarged to 8 cm. below the right costal margin; it was firm and its surface irregular. The urine gave an orange colour with Benedict's solution, and Rothera's test for acetone was strongly positive. His blood pressure was 130/75 mm. Hg; temperature 99° F. (37.2° C.).

A radiograph of the chest showed an opacity in the right cardiophrenic angle due to collapse of the right lower lobe; the right paratracheal lymph nodes were enlarged. Tomography of the chest revealed a mass 4 cm. in diameter in the right cardiophrenic angle with narrowing of the right lower lobe bronchus. At bronchoscopy rigidity of the right main bronchus with narrowing of the right lower lobe bronchus was demonstrated, but no neoplasm was identified; biopsy showed normal bronchial mucosa. Liver needle biopsy contained metastatic carcinoma, and the bone marrow also contained carcinoma cells.

Liver-function tests showed serum bilirubin 0.4 mg. per 100 ml., thymol turbidity less than 1 unit, serum alkaline phosphatase 28 King-Armstrong units, serum proteins 5.4 g. per 100 ml. (albumin 3.7 g., globulin 1.7 g.), bromsulphthalein excretion normal, serum iron 115 µg. per 100 ml., and prothrombin efficiency 100%. The urine was free from bile and contained only traces of urobilinogen.

Other investigations performed were: fasting blood sugar 441 mg. per 100 ml. (following 50 g. of glucose by mouth the blood sugar rose to 483 mg. after 1½ hours, and was 378 mg. after 2½ hours); 24-hour urinary excretion of 17-ketosteroids 50.4 mg., of 17-ketogenic steroids 138 mg., and of pregnanediol 8.7 mg.; serum sodium 152 mEq/l., serum potassium 4.4 mEq/l., serum chloride 99 mEq/l., and plasma alkali reserve (four days after admission) 28 mEq/l.; blood urea 40 mg. per 100 ml.

The haemoglobin was 10 g. per 100 ml., W.B.C.s 4,000 per c.mm. (polymorphs 68%, lymphocytes 28%, monocytes 4%). The Wassermann reaction was negative and an electrocardiogram showed no abnormality.

Skin biopsy revealed atrophy of the Malpighian layer and some hyperkeratinization of the epidermis. The deeper layers of the epidermal cells were heavily pigmented with melanin.

Progress.—On a diet containing 160 g. of carbohydrate a day it was possible to control his diabetes with 88 units of insulin zinc suspension. The patient slowly deteriorated, however; he continued to lose flesh, his oedema increased, he developed ascites, and the liver became larger and more irregular. There was increasing evidence of peripheral neuritis with weakness of the arms and legs, loss of deep reflexes, and absence of sensation over the hands and feet. On June 16 he was noticed to be jaundiced and to have a petechial rash. He died on June 23.

Special Investigations.—The daily urinary 17-ketosteroid and 17-ketogenic steroid urinary excretion from June 10 until his death on June 23 is shown in the Chart. Cortisone, 50 mg. six-hourly by mouth, was administered for 48 hours on June 14 and 15, and corticotrophin of known potency, 25 mg., was given six-hourly intramuscularly for 48 hours on June 21 and 22. It will be seen that the 17-ketosteroid excretion showed no great variation, and that the 17-ketogenic steroid excretion remained between 106 and 159 mg.